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METHODS AND COMPOSITIONS FOR IMPROVING DIGESTION AND ABSORPTION IN THE SMALL INTESTINE

by

Henry C. Lin, M.D.

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Attorneys

Pretty, Schroeder & Poplawski, P.C.
444 South Flower Street, Suite 2000
Los Angeles, California 90071

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METHODS AND COMPOSITIONS FOR IMPROVING DIGESTION AND ABSORPTION IN THE SMALL INTESTINE

This application is a continuation-in-part of U.S. Patent Application Serial No. 09/359,583, filed on July 22, 1999, which is a continuation of U.S. Patent Application Serial No. 08/832,307, filed on April 3, 1997, which is a continuation of U.S. Patent Application Serial No. 08/442,843, filed on May 17,1995.

FIELD OF THE INVENTION

The present invention relates to methods and pharmaceutical compositions for controlling the presentation of lumenal content in the gastrointestinal tract.

BACKGROUND OF THE INVENTION

A principal function of the gastrointestinal tract is to process and absorb food. The stomach, which is both a storage and digestive organ, works to optimize the conditions for the digestion and absorption of food in the small intestine. Following the stomach and preceding the large bowel (colon) is the small intestine, which comprises three regions: the duodenum, jejunum, and ileum. A major function of the small intestine is one of absorption of digested nutrients.

The passage of a meal through the gastrointestinal tract, which leads to digestion and absorption of nutrients, is controlled by a complex system of inhibitory and stimulatory motility mechanisms which are set in motion by the composition of the meal ingested. Specific receptors for fats and proteins, and the osmolality, acidity and particle size of the meal activate propulsive and inhibitory reactions, which modulate transit and thus absorption. In normal human subjects, the mechanisms that regulate gastrointestinal transit can, under some circumstances, be sensitized or desensitized in response to the subject's recent dietary history. (K.M. Cunningham *et al.*, *Gastrointestinal adaptation to diets of differing fat composition in human volunteers*, Gut 32(5):483-86 [1991]).

The rate of transit through the small intestine is of great significance for the rate and extent of absorption from the small intestine. Disruption of the normal

digestive and absorptive processes frequently manifests as a variety of syndromes, such as, for example malnutrition, weight loss, diarrhea, steatorrhea, vitamin deficiency, electrolyte imbalance, and the like. Chronic diarrhea is a common problem found in a variety of gastrointestinal disorders where water, solutes and nutrients are malabsorbed (Read, N.W., Diarrhee motrice, Clin. Gastroenterol. 15: 657-86 [1986]). Specifically, conditions such as short bowel syndrome, postgastrectomy dumping and ileal resection may lead to symptoms such as postprandial distension, cramping, abdominal pain, gaseousness, nausea, palpitations, flushing, steatorrhea or weight loss. These symptoms may persist despite the use of anti-diarrheal medications, anticholinergic agents (Ivey, KJ., *Are anticholinergics of use in the irritable bowel syndrome?*, Gastroenterology 68: 1300-07 [1975]), somatostatin analogues (Reasbeck PG, and AM Van Rij, *The effect of somatostatin on dumping after surgery: A preliminary report*, Surgery 1986; 99: 462-468 [1986]), conjugated bile acid replacement therapy (C. Gruy-Kapral *et al.*, *Conjugated bile acid replacement therapy for short-bowel syndrome*, Gastroenterol. 116:15-21 [1999]), or large quantities of opiates (O'Brien, J.D. *et al.*, *Effect of codeine and loperamide on upper intestinal transit and absorption in normal subjects and patients with postvagotomy diarrhea*, Gut 19: 312-18 [1988]). Additionally, even with treatment, fecal loss of water, solutes and nutrients may still be so excessive in some patients that long term use of parenteral fluids and nutrition may be required for survival (Rombeau, J.L. and R.H. Rolandelli, *Enteral and parenteral nutrition in patients with enteric fistulas and short bowel syndrome*, Surg. Clin. North Am. 67:551-571 [1989]).

The small intestine is also an important site for the absorption of pharmacological agents. The proximal part of the small intestine has the greatest capacity for absorption of drugs. Intestinal absorption of drugs is influenced to a great extent by many of the same basic factors that affect the digestion and absorption of nutrients, water and electrolytes.

Absorption of a drug in the gastrointestinal tract is a function of characteristics of the drug, such as its molecular structure, as well as attributes of the gastrointestinal tract. The rate of absorption of certain drugs, which are absorbed slowly and usually incompletely, varies according to the small intestinal transit time. Intestinal transit is important in the design of pharmaceutical preparations, especially when the absorption site of a drug is located in a particular segment of the gastrointestinal tract.

Many drugs and dosage formulations have been and continue to be developed because of the need to overcome the physiological and physicochemical limitations associated with drug delivery such as poor stability, short biological half-life, inefficient absorption and poor bioavailability. Applications of controlled release technology have moved towards control of absorption via regulation of the input to the gastrointestinal tract. However, recent pharmaceutical attempts to alter gastric emptying and small intestinal transit times have not been very successful. (Khosla and Davis, *J. Pharm. Pharmacol.* 39:47-49 [1987]; Davis *et al.*, *Pharm. Res.* 3:208-213 [1986]).

For drug absorption to proceed efficiently, the drug must first arrive at a normal absorbing surface in a form suitable for absorption; it must remain there long enough in a form and in a concentration that enhance absorption; and it must be absorbed by a normal epithelial cell without being metabolized by that cell. Accordingly, considerable advantage would be obtained if a pharmaceutical dosage form could be retained for a longer period of time within the stomach and/or the small intestine for proper absorption to occur.

The period of time during which nutrients and/or drugs are in contact with the mucosa of the small intestine is crucial for the efficacy of digestion and absorption. Inadequate residence time can lead to fecal loss of nutrients and diarrhea. Therefore, modulation of the motility rate and transit time of nutrients and/or pharmacologically active agents through the gastrointestinal tract will ensure optimal utilization of the absorptive surface, as well as prevent transport mechanisms from being overloaded

(which could occur if substrates were passed on too rapidly and exceeded the absorptive capacity of already maximally loaded surfaces in the small intestine).

The speed of transit through the small intestine is normally regulated by inhibitory mechanisms located in the proximal and distal small intestine known as the jejunal brake and the ileal brake. Inhibitory feedback is activated to slow transit when end products of digestion make contact with nutrient sensors of the small intestine. Specifically, jejunal and ileal brakes slow transit by the release of gut peptides such as peptide YY and by the activation of neural pathways such as those involving endogenous opioids. Transit is then slowed by the stimulation of nonpropagative intestinal contractions which inhibit movement of the lumenal content. The removal or impairment of these inhibitory mechanisms can lead to abnormally rapid transit. For example, in patients with a history of resection of the terminal ileum, intestinal transit may become uncontrolled and abnormally accelerated when the ileal brake is no longer intact. Time for processing of food may then be so reduced that few end products of digestion are available to trigger the jejunal brake as the remaining inhibitory mechanism.

Thus, a need exists for optimizing absorption of ingested nutrients and/or pharmacologically active agents in the small intestine to prevent and/or reduce ineffectiveness thereof due to malabsorption. A need also exists for means to enhance the bioavailability and effectiveness of pharmacologically active agents. The present invention satisfies these needs and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides methods and compositions for slowing gastrointestinal transit and prolonging residence time to optimize presentation and absorption of ingested nutrients and/or pharmacologically active agents in the small intestine to prevent and/or reduce ineffectiveness thereof due to malabsorption.

The present invention further provides methods and compositions for enhancing the bioavailability and therapeutic effectiveness of pharmacologically active agents.

DETAILED DESCRIPTION OF THE INVENTION

Important steps in dietary lipid absorption begin in the stomach, where an intricate control system of inhibitory and stimulatory motility mechanisms are set in motion by the composition of the meal ingested. These mechanisms prevent too rapid emptying of gastric contents into the duodenum, which would overwhelm its capacity for lipid or fat absorption. Such preventative mechanisms ensure a maximum interface of the water-insoluble lipid with the aqueous contents of the intestinal tract.

The next step in absorption of fats or lipids occurs upon their entry into the small intestine. In the early portion of the small intestine, specific receptors for fats and proteins,and the osmolality, acidity and the particle size of the meal activate propulsive and inhibitory reactions (i.e., ileal braking), which modulate their transit and absorption. The rate of passage through the small intestine (i.e., intestinal transit time) is of great significance for the rate and extent of absorption from the small intestine.

In the duodenum, the fats which have been released from the stomach encounter bile acids and pancreatic enzymes. The function of the bile acids is to render soluble the insoluble triglyceride molecules.

The intestinal absorption of lipids is normally very efficient over wide ranges of dietary fat intake. A normal person generally absorbs approximately 95-98% of dietary lipid. When the normal digestive and absorptive processes are impaired, malabsorption syndromes frequently ensue.

Malabsorption syndromes include a large heterogeneous group of gastrointestinal disorders with the common characteristic of failure to assimilate ingested substances normally. The defect is characterized by decreased or impaired function of

almost any organ of the gut, including the liver, biliary tract, pancreas, and lymphatic system, as well as the intestine. The clinical manifestations may vary from a severe symptom complex of rapid intestinal transit, dumping syndrome, diarrhea, weight loss, distention, steatorrhea, and asthenia to symptoms of specific nutrient deficiencies (i.e., malnutrition).

Examples of gastrointestinal disorders that frequently manifest as one or more malabsorption syndromes are postgastrectomy syndrome, dumping syndrome, AIDS-associated chronic diarrhea, diabetes-associated diarrhea, postvagotomy diarrhea, bariatric surgery-associated diarrhea (including obesity surgeries: gastric bypass, gastroplasties and intestinal bypass), short bowel syndrome (including resection of the small intestine after trauma, radiation induced complications, Crohn's disease, infarction of the intestine from vascular occlusion), tube-feeding related diarrhea, chronic secretory diarrhea, carcinoid syndrome-associated diarrhea, gastrointestinal peptide tumors, endocrine tumors, chronic diarrhea associated with thyroid disorders, chronic diarrhea in bacterial overgrowth, chronic diarrhea in gastrinoma, choleraic diarrhea, chronic diarrhea in giardiasis, antibiotic-associated chronic diarrhea, diarrhea-predominant irritable bowel syndrome, chronic diarrhea associated with maldigestion and malabsorption, chronic diarrhea in idiopathic primary gastrointestinal motility disorders, chronic diarrhea associated with collagenous colitis, surgery-associated acute diarrhea, antibiotic-associated acute diarrhea, infection-associated acute infectious diarrhea, and the like.

The rate at which food passes through the gastrointestinal tract is an important factor that affects the absorptive capacity and the outcome following gastric surgery and/or intestinal resection. Resection of extensive sections of bowel as well as loss of absorptive surface secondary to diseased small bowel mucosa can lead to specific malabsorption syndromes. Resection or disease of large amounts of terminal ileum are known to cause vitamin B12 and bile acid deficiencies, which, in turn, can lead to fat and other fat-soluble substances being less well absorbed. Bypassed loops of bowel, created by either surgery or fistula formation, and strictures can result in blind loop syndromes with bacterial overgrowth and subsequent malabsorption.

Malnutrition is a common problem in patients with inflammatory bowel diseases such as, for example, Crohn's disease or ulcerative colitis. Weight loss is found in 70-80% of patients with Crohn's disease and 18-62% of patients with ulcerative colitis.

The role of nutritional support as a primary therapy for inflammatory bowel diseases is not well established. Given the natural history of inflammatory bowel diseases, with frequent relapses and spontaneous remissions, and the difficulty and variability in quantifying disease activity, it has been difficult to design clinical trials that definitively establish the role of nutrition as a primary therapy for inflammatory bowel diseases. The use of elemental diets as primary therapy for inflammatory bowel diseases has also been examined. Parenteral nutrition and elemental diets appear to have limited roles in the long-term treatment of patients with inflammatory bowel diseases.

Short bowel syndrome generally refers to a condition in which less than 150 cm of remaining small bowel is associated with a massive loss of absorptive capacity. It is characterized by severe diarrhea and malabsorption. Patients with short bowel syndrome often experience malabsorption of protein, carbohydrate and fat resulting in calorie depletion and steatorrhea.

The most important therapeutic objective in the management of short bowel is to maintain the patient's nutritional status. By necessity, it is achieved primarily by parenteral nutrition support in the early postoperative period. Enteral nutrition support can be started early after operation when the ileus has resolved. Maximization of enteral absorption of nutrients is important for long-term survival. Generally, such maximization requires that the enteral intake greatly exceed the absorptive needs to ensure that the nutritional requirements are met.

Functional pancreatic insufficiency may also cause steatorrhea after gastric resection. Steatorrhea is the presence of excess fat in the feces. It is usually caused by a defect in gastrointestinal digestion and/or absorption. Steatorrhea rarely exists without malabsorption of other substances. For example, conditions such as osteomalacia related

to calcium and vitamin D deficiency or anemia due to selective iron or B12 deficiencies are often associated with the malabsorption that occurs with steatorrhea. Weight loss occurs because of a loss of nutrients and energy. Diarrhea is another major symptom associated with steatorrhea. It is present in 80-97% of patients with malabsorption.

Dumping syndrome is one of the most common causes of morbidity after gastric surgery. This syndrome is characterized by both gastrointestinal and vasomotor symptoms. Gastrointestinal symptoms include postprandial fullness, crampy abdominal pain, nausea, vomiting and explosive diarrhea. Vasomotor symptoms include, diaphoresis, weakness, dizziness, flushing, palpitations, and an intense desire to lie down. Patients with severe dumping symptoms may limit their food intake to minimize symptoms and as a result lose weight and become malnourished. In severe cases, as a last resort surgical treatment of dumping syndrome has been utilized.

Pharmaceutical treatment for severe dumping includes octreotide acetate (Sandoz), a long acting somatostatin analogue, which has been used with some success. Octreotide is administered subcutaneously and acts to slow gastric emptying, inhibit insulin release, and decrease enteric peptide secretion. Octreotide, unfortunately, is accompanied by several complications, which include injection site pain, tachyphylaxis, iatrogenic diabetes, malabsorption and cholelithiasis.

Diarrhea is a common problem after any abdominal operation. Treatment includes simple dietary changes, opiates and/or opiod-type drugs such as Lomotil or paregoric, antidiarrheal agents such as Diasorb (attapulgite), Donnagel (kaolin, hydroscyamine sulfate, atropine sulfate and scopalamine hydrobromide), Kaopectate, Motofen (difenoxin hydrochloride and atropine sulfate) and Pepto-Bismol for inhibitory effect on intestinal transit. Each modality of treatment, however, has had limited success and with the exception of dietary changes, all have negative side effects associated with use.

Diarrhea is also a common complication associated with enteral feeding. Multiple etiologies for diarrhea are postulated, and its genesis may be a multifactorial process (Edes et al., *Am. J. Med.* 88:91-93 (1990). Causes include concurrent use of antibiotics or other diarrhea-inducing medications, altered bacterial flora, formula composition, rate of infusion, hypoalbuminemia, and enteral formula contamination. The composition of formula may also affect the incidence of diarrhea. The use of fiber-containing formulas to control diarrhea related to tube feeding is unsettled (Frankenfield *et al., Am. J. Clin. Nutr.* 50:553-558 [1989]).

A tremendous amount of research has been undertaken in attempting to elucidate the role of nutrition and absorption in gastrointestinal disorders. Despite this research, few standards of care presently exist for the use of nutrition and absorption in most aspects of these disorders.

Accordingly, the present invention provides methods of slowing gastrointestinal transit to prolong the residence time of a substance in the small intestine of a subject for an amount of time sufficient for digestion and absorption of the substance to occur therein. Invention methods comprise administering to a subject a composition comprising an active lipid in an amount effective to slow the transit of said substance through the small intestine for an amount of time sufficient for absorption of said substance to occur therein.

The invention contemplates a range of optimal residence times which are dependent upon the character of the substance (i.e., nutrients, pharmacologically active agents). As used herein, "substance" encompasses the lumenal content of the gastrointestinal tract which includes, for example, digested and partially digested foods and nutrients, dissolved and/or solubilized pharmacologically active agents as well as incompletely dissolved and/or solubilized forms thereof, electrolyte-containing lumenal fluids, and the like.

The small intestinal residence time for optimal absorption of digested foods and nutrients can be calculated using an average orocecal transit time as a reference. The normal orocecal transit time is approximately 2-3 hours in the fasted state. The inventive composition should target an intestinal residence within the same average time frame of approximately 2-3 hours.

The pharmaceutical industry has published a great deal of information on the dissolution time for individual pharmacologically active agents and compounds. Such information is found in the numerous pharmacological publications which are readily available to those of skill in the art. For example, if the *in vitro* model for dissolution and release of agent "X" is 4 hours, then the small intestinal residence time for optimal absorption of agent "X" would be at least 4 hours and would also include additional time allowing for gastric emptying to occur *in vivo*. Thus, for pharmacologically active agents, the appropriate residence time is dependent on the time for release of the active agent.

As used herein, "digestion" encompasses the process of breaking down large molecules into their smaller component molecules.

As used herein, "absorption" encompasses the transport of a substance from the intestinal lumen through the barrier of the mucosal epithelial cells into the blood and/or lymphatic systems.

As used herein, "pharmacological agent" encompasses any substance used to treat a disorder, abnormal condition, discomfort, wound, lesion, or injury, of a physical, biochemical, mental, emotional or affective nature. Examples of pharmacological agents include, but are not limited to, somatostatin analogues, insulin release inhibitors, anti-diarrheal agents, antibiotics, fiber, electrolytes, analgesics, antipyretics, migraine treatment, migraine prophylaxis, antifungal agents, antiviral agents, Quinolones, AIDS therapeutic agents, anti-infectives, aminoglycosides, antispasmodics, parasympathomimetics, anti-tuberculous agents, anti-malarial agents, accines, anti-parasitic agents, cephalosporins, macrolides, azalides, tetracyclines, penicillins, anti-

arthritic therapy agents, gout therapy agents, nonsteroidal anti-inflammatory agents, gold compounds, antianemic agents, antianginal agents, antiarrhythmics, anticoagulants, post-MI agents, vasodilators, beta-adrenergic blockers, calcium channel blockers, nitrates, thrombolytic agents, anticoagulants, antifibrolytic agents, hemorrheologic agents, antiplatelet agents, vitamins, antihemophilic agents, heart failure agents, ACE inhibitors, cardiac glycosides, blood flow modifying agents, bile salts, growth promoting agents, growth suppressive agents, sympathomimetics, inotropic agents, antihypertensive agents, central alpha-adrenergic agonists, peripheral vasodilator, sympatholytics, diuretics, diuretic combinations, mineral supplements, hypolipedemic agents, acne treatments, antidiarrheal agents, antinauseants, antiemetics, antispasmodics, antiulcer, antireflux agents, appetite suppressants, appetite enhancers, gallstone-dissolving agents, gastrointestinal anti-inflammatory agents, antacids, antiflatulents, anti-gas agents, laxatives, stool softeners, digestants, digestive enzymes, enzyme supplements, alzheimer's therapy, anticonvulsants, antiparkinson agents, sedatives, benzodiazepines, benzodiazepine receptor antagonists, receptor agonists, receptor antagonists, interferons, immunosuppressive therapy, immunomodulatory agents, muscle relaxants, hypnotics, antianxiety agents, antimanic agents, antidepressants, antiobesity agents, behavior modifiers, psychostimulants, neurostimulants, abuse deterrents, anxiolytics, antipsychotics, antianaphylactic agents, antihistamines, antipruritics, anti-inflammatory agents, bronchodilators, antiasthmatic agents, cystic fibrosis therapy agents, mast-cell stabilizers, steroids, xanthines, anticholinergic agents, bioactive peptides, polypeptides, hormones, drugs acting at neuroeffector junctional sites, prostaglandins, narcotics, hypnotics, alcohols, psychiatric therapy agents, anti-cancer chemotherapy agents, drugs affecting motility, oral hypoglycemics, androgens, estrogens, nutriceuticals, herbal medications, insulin, serotonin receptor agonist, serotonin receptor antagonists, alternative medicines, amino acids, dietary supplements, analeptic agents, respiratory agents, cold remedies, cough suppressants, antimycotics, bronchodilators, constipation aids, contraceptives, decongestants, expectorants, motion sickness products, homeopathic preparations.

The inventive compositions comprise an active lipid and a pharmaceutically acceptable carrier. A major function of the inventive compositions is to slow gastrointestinal transit and control gastrointestinal intestinal residence time of a substance to enable substantial completion of lumenal and mucosal events required for absorption of the substance to occur in the small intestine. Of equal significance is the function of the inventive compositions to control the presentation of a substance to a desired region of the small intestine for absorption.

In a preferred embodiment, the inventive compositions limit the presentation of a substance to the proximal region of the small intestine for absorption.

As used herein, "active lipid" encompasses a digested or substantially digested molecule having a structure and function substantially similar to a hydrolyzed end-product of fat digestion. Examples of hydrolyzed end products are molecules such as glycerol and fatty acids.

In a preferred embodiment, the active lipid comprises a saturated or unsaturated fatty acid. Fatty acids contemplated by the invention include fatty acids having between 4 and 24 carbon atoms.

Examples of fatty acids contemplated for use in the practice of the present invention include caprolic acid, caprulic acid, capric acid, lauric acid, myristic acid, oleic acid, palmitic acid, stearic acid, palmitoleic acid, linoleic acid, linolenic acid, *trans*-hexadecanoic acid, elaidic acid, columbinic acid, arachidic acid, behenic acid eicosenoic acid, erucic acid, bressidic acid, cetoleic acid, nervonic acid, Mead acid, arachidonic acid, timnodonic acid, clupanodonic acid, docosahexaenoic acid, and the like. In a preferred embodiment, the active lipid comprises oleic acid.

Also preferred are active lipids in the form of pharmaceutically acceptable salts of hydrolyzed fats, including salts of fatty acids. Sodium or potassium salts are preferred, but salts formed with other pharmaceutically acceptable cations are also useful.

Useful examples include sodium- or potassium salts of caprolate, caprulate, caprate, laurate, myristate, oleate, palmitate, stearate, palmitolate, linolate, linolenate, *trans*-hexadecanoate, elaidate, columbinate, arachidate, behenate, eicosenoate, erucate, bressidate, cetoleate, nervonate, arachidonate, timnodonate, clupanodonate, docosahexaenoate, and the like. In a preferred embodiment, the active lipid comprises an oleate salt.

The active lipids suitable for use with this invention are employed in well dispersed form in a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" encompasses any of the standard pharmaceutical carriers known to those of skill in the art. For example, one useful carrier is a commercially available emulsion, Ensure®, but active lipids, such as oleate or oleic acid are also dispersible in gravies, dressings, sauces or other comestible carriers. Dispersion can be accomplished in various ways. The first is that of a solution. Lipids can be held in solution if the solution has the properties of bile (i.e., solution of mixed micelles with bile salt added), or the solution has the properties of a detergent (e.g., pH 9.6 carbonate buffer) or a solvent (e.g., solution of Tween). The second is an emulsion which is a 2-phase system in which one liquid is dispersed in the form of small globules throughout another liquid that is immiscible with the first liquid (Swinyard and Lowenthal, "Pharmaceutical Necessities" *REMINGTON'S PHARMACEUTICAL SCIENCES*, 17th ed., AR Gennaro (Ed), Philadelphia College of Pharmacy and Science, 1985 p.1296). The third is a suspension with dispersed solids (e.g., microcrystalline suspension). Additionally, any emulsifying and suspending agent that is acceptable for human consumption can be used as a vehicle for dispersion of the composition. For example, gum acacia, agar, sodium alginate, bentonite, carbomer, carboxymethylcellulose, carrageenan, powdered cellulose, cholesterol, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, octoxynol 9, oleyl alcohol, polyvinyl alcohol, povidone, propylene glycol monostearate, sodium lauryl sulfate, sorbitan esters, stearyl alcohol, tragacanth, xantham gum, chondrus, glycerin, trolamine, coconut oil, propylene glycol, thyl alcoholmalt and malt extract. Any of these solutions, emulsions or suspensions can be

incorporated into capsules, or a microsphere or particle (coated or not) contained in a capsule.

The compositions of the invention containing the active lipid may be in a form suitable for oral or enteral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs or enteral formulas. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Compositions may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release. Other techniques for controlled release compositions, such as those described in the U.S. Pat. Nos. 4,193,985; and 4,690,822; 4,572,833 may be used in the formulation of the inventive compositions.

An effective amount of active lipid is any amount that is effective to slow gastrointestinal transit and control presentation of a substance to a desired region of the small intestine. For example, an effective amount of active lipid, as contemplated by the instant invention, is any amount of active lipid that can trigger any or all of the following reflexes: intestino-lower esophageal sphincter (relaxation of LES); intestino-gastric feedback (inhibition of gastric emptying); intestino-intestinal feedback (ileo-jejunal feedback/ileal brake, jejuno-jejunal feedback/jejunal brake, intestino-CNS feedback (for example, intensifying intestinal signalling of satiety`); intestino-pancreatic feedback (control of exocrine enzyme output); intestino-biliary feedback (control of bile flow); intestino-mesenteric blood flow feedback (for the control of mucosal hyperemia); intestino-colonic feedback (so called gastro-colonic reflex whereby the colon contracts in response to nutrients in the proximal small intestine).

Methods of administration are well known to those of skill in the art and include, but are not limited to oral administration, parenteral administration and enteral administration. In a preferred embodiment, the composition of the invention is administered in a load-dependent manner which ensures that the dispersion of active lipid

is presented to the entire length of the small intestine. Administration is in one or more doses such that the desired effect is produced. In some preferred embodiments, the load of active lipid per dose is from about 0.5 grams to about 2.0 grams, but can range up to about 25 grams per dose as needed. Generally, patients respond well to the most preferred amount of active lipid, which is in the range of about 1.6 to 3.2 grams. For patients who fail to respond to this dose range, a dose between 6 and 8 grams is typically effective.

In order to stretch biologic activity so that one has a convenient, daily dosage regimen, the present invention contemplates that the inventive compositions are administered prior to ingestion of the food, nutrient and/or pharmacologically active agent. In a preferred embodiment, the inventive compositions (depending on the formulation) are administered up to a period of 24 hours prior to ingestion of the food, nutrient and/or pharmacologically active agent, but most preferably between about 60 to 5 minutes before ingestion. The period of time prior to ingestion is determined on the precise formulation of the composition. For example, if the formulation incorporates a controlled release system, the duration of release and activation of the active lipid will determine the time for administration of the composition. Sustained release formulation of the composition is useful to ensure that the feedback effect is sustained.

Sequential dosing is especially useful for patients with short bowel syndrome or others with abnormally rapid intestinal transit times. In these patients, the first preprandial administration of the active lipid occurs in a condition of uncontrolled intestinal transit that can fail to permit optimal effectiveness of the active lipid. A second (or more) preprandial administration(s) timed about fifteen minutes after the first or previous administration and about fifteen minutes before the meal enhances the patient's control of intestinal lumenal contents and the effectiveness of the active lipid agent in accordance with the inventive methods. Normalization of nutrient absorption and bowel control throughout the day, including during the patient's extended sleeping hours, is best achieved by a dietary regimen of three major meals with about five snacks interspersed between them, including importantly, a pre-bedtime snack; administration

of a dose of the inventive composition should occur before each meal or snack as described above.

Treatment with the inventive compositions in accordance with the inventive methods can be of singular occurrence or can be continued indefinitely as needed. For example, patients deprived of food for an extended period (e.g., due to a surgical intervention or prolonged starvation), upon the reintroduction of ingestible food, may benefit from administration of the inventive compositions before meals on a temporary basis to facilitate a nutrient adaptive response to normal feeding. On the other hand some patients, for example those with surgically altered intestinal tracts (e.g., ileal resection), may benefit from continued pre-prandial treatment in accordance with the inventive methods for an indefinite period. However, clinical experience with such patients for over six years has demonstrated that after prolonged treatment there is at least a potential for an adaptive sensory feedback response that may allow them to discontinue treatment for a number of days without a recurrence of postprandial diarrhea or intestinal dumping.

The use of compositions of the present invention in enteral feeding contemplates adding the composition directly to the feeding formula. The composition can either be compounded as needed into the enteral formula when the rate of formula delivery is known (i.e., add just enough composition to deliver the load of active lipids). Alternatively, the composition of the invention can be compounded at the factory so that the enteral formulas are produced having different concentrations of the composition and can be used according to the rate of formula delivery (i.e., higher concentration of composition for lower rate of delivery).

If the inventive composition were to be added to an enteral formula and the formula is continuously delivered into the small intestine, the composition that is initially presented with the nutrient formula would be slowing the transit of nutrients that are delivered later. Except for the start of feeding when transit may be too rapid because

the inhibitory feedback from the composition has yet to be fully activated, once equilibrium is established, it is no longer logistically an issue of delivering the composition as a premeal although the physiologic principle is still the same.

Before dietary fats can be absorbed, the motor activities of the small intestine in the postprandial period must first move the output from the stomach to the appropriate absorptive sites of the small intestine. To achieve the goal of optimizing the movement of a substance through the small intestine, the temporal and spatial patterns of intestinal motility are specifically controlled by the nutrients of the lumenal content.

Without wishing to be bound by any theory, it is presently believed that early in gastric emptying, before inhibitory feedback is activated, the load of fat entering the small intestine may be variable and dependent on the load of fat in the meal. Thus, while exposure to fat may be limited to the proximal small bowel after a small load, a larger load, by overwhelming more proximal absorptive sites, may spill further along the small bowel to expose the distal small bowel to fat. Thus, the response of the duodenum to fat limits the spread of fat so that more absorption can be completed in the proximal small intestine and less in the distal small intestine. Furthermore, since the speed of movement of lumenal fat must decrease when more fat enters the duodenum, in order to avoid steatorrhea, intestinal transit is inhibited in a load-dependent fashion by fat. This precise regulation of intestinal transit occurs whether the region of exposure to fat is confined to the proximal gut or extended to the distal gut.

In accordance with the present invention it has been observed that inhibition of intestinal transit by fat depends on the load of fat entering the small intestine. More specifically, that intestinal transit is inhibited by fat in a load-dependent fashion whether the nutrient is confined to the proximal segment of the small bowel or allowed access to the whole gut.

Accordingly, the present invention provides a method of slowing gastrointestinal transit in a subject having a gastrointestinal disorder, said method

comprising administering to said subject a composition comprising an active lipid in an amount sufficient to prolong the residence time of a substance in the small intestine.

Invention methods and compositions are useful in the management of nutritional and absorption in subjects having a variety of gastrointestinal symptoms such as, rapid intestinal transit, dumping syndrome, diarrhea, weight loss, distention, steatorrhea, and asthenia to symptoms of specific nutrient deficiencies (i.e., malnutrition).

Examples of gastrointestinal disorders that invention methods and compositions are therapeutic include postgastrectomy syndrome, dumping syndrome, AIDS-associated chronic diarrhea, diabetes-associated diarrhea, postvagotomy diarrhea, bariatric surgery-associated diarrhea (including obesity surgeries: gastric bypass, gastroplasties and intestinal bypass), short bowel syndrome (including resection of the small intestine after trauma, radiation induced complications, Crohn's disease, infarction of the intestine from vascular occlusion), tube-feeding related diarrhea, chronic secretory diarrhea, carcinoid syndrome-associated diarrhea, gastrointestinal peptide tumors, endocrine tumors, chronic diarrhea associated with thyroid disorders, chronic diarrhea in bacterial overgrowth, chronic diarrhea in gastrinoma, choleraic diarrhea, chronic diarrhea in giardiasis, antibiotic-associated chronic diarrhea, diarrhea-predominant irritable bowel syndrome, chronic diarrhea associated with maldigestion and malabsorption, chronic diarrhea in idiopathic primary gastrointestinal motility disorders, chronic diarrhea associated with collagenous colitis, surgery-associated acute diarrhea, antibiotic-associated acute diarrhea, infection-associated acute infectious diarrhea, and the like.

The instant invention further provides a method and composition for treating diarrhea in a subject, said method comprising administering to said subject a composition comprising an active lipid in an amount sufficient to prolong the residence time of the lumenal contents of the small intestine. The inventive composition can be delivered as a single unit, multiple unit (for more prolonged effect via enterically coated or sustained release forms) or in a liquid form.

Since cholesterol and triglycerides are so insoluble in plasma, after mucosal absorption of lipids, the transport of these lipids from the intestine to the liver occurs through lipoproteins called chylomicrons.

While fat absorption from the lumen is rate-limiting for the proximal half of the small intestine, chylomicron synthesis or release is rate-limiting for the distal one half of the small intestine. As a result, chylomicrons formed by the distal small intestine are larger than those from the proximal small intestine (Wu, 1975). In the capillary bed of the peripheral circulatory system, the enzyme lipoprotein lipase hydrolyzes and removes most of the triglycerides from the chylomicron. The lipoprotein that remains, now rich in cholesterol esters and potentially atherogenic, is called a chylomicron remnant. This postprandial lipoprotein is then removed from the circulation by the liver (Zilversmit, *Circulation* 60(3):473 [1979]).

Elevated levels of atherogenic serum lipids have been directly correlated with atherosclerosis (Keinke *et al.*, *Q. J. Exp. Physiol.* 69:781-795 [1984]).

The present invention provides a novel method to minimize atherogenic postprandial lipemia by optimizing proximal fat absorption. In other words, the present invention provides a novel method by which atherogenic serum lipids can be controlled preabsorptively by the fed motility response of the small intestine to lumenal fat.

Preabsorptive control depends on the triggering of a specific pattern of proximal intestinal motility which slows transit to minimize the spread of fat into the distal gut. After a small meal of cholesterol-containing, fatty foods, the small intestine limits the site of fat absorption to the proximal small intestine by generating nonpropagated motility to slow intestinal transit. Since chylomicrons produced by the proximal small intestine are small in size, the size distribution of postprandial lipoproteins is shifted to minimize postprandial lipemia. However, during gorging of a high cholesterol, high fat meal, the ability of the small intestine to optimize proximal fat absorption is reduced by the time-dependent fading of the effect of fat on nonpropagated

motility. As a result, after the first 1-2 hours, faster intestinal transit works to displace lumenal fat into the distal small intestine where large, cholesterol-enriched, atherogenic chylomicrons are formed and released into the circulation.

In addition to the dietary effects on intestinal transit, studies suggest that nicotine inhibits intestinal motility. (McGill [1979]; Maida [1990]) (Booyse [1981]) (Carlson [1970]). In the postprandial situation, this nicotine-related inhibitory effect alters the potentially protective, braking or nonpropagated pattern of motility. As a result, nicotine may facilitate the spreading of ingested lipids into the distal small intestine and impair the preabsorptive control of lipids. The methods of the present invention provide means to minimize the nicotine-induced inhibition of this postprandial response and to maximize proximal fat absorption.

Oral pharmaceutical preparations account for more than 80% of all drugs prescribed. It is essential, therefore, to control the multiple factors that influence their intestinal absorption as a determinant of ultimate therapeutic effectiveness.

Disintegration and dissolution are factors determining drug absorption that takes place only after a drug is in solution. Drugs ingested in solid form must first dissolve in the gastrointestinal fluid before they can be absorbed, and tablets must disintegrate before they can dissolve. The dissolution of a drug in the gastrointestinal tract is often the rate-limiting step governing its bioavailability. In any given drug, there can be a 2- to 5-fold difference in the rate or extent of gastrointestinal absorption, depending on the dosage or its formulation.

The rate of gastric emptying bears directly on the absorption of ingested drugs and on their bioavailability. Some drugs are metabolized or degraded in the stomach, and delayed gastric emptying reduces the amount of active drug available for absorption.

The pharmaceutical industry has developed all sorts of slow and/or

sustained-release technology. These efforts have been directed to delaying gastric emptying. Sustained-release formulations employ several methods. The most common is a tablet containing an insoluble core; a drug applied to the outside layer is released soon after the medication is ingested, but drug trapped inside the core is released more slowly. Capsules containing multiparticulate units of drug with coatings that dissolve at different rates are designed to give a sustained-release effect. However, the basic problem with sustained-release medications is the considerable variability in their absorption due to the inability to monitor the individual's ingestion of the medication and thus, inability to control transit. Accordingly, slow release of drug in the absence of slow transit in the gut is meaningless.

The instant invention solves the bioavailability problem in this instance. The methods and compositions of this invention enable one to manipulate the balance of dissolution and gastrointestinal transit by increasing gastrointestinal residence time.

To facilitate drug absorption in the proximal small intestine, the present invention provides a method for prolonging the gastrointestinal residence time which will allow drugs in any dosage form to more completely dissolve and be absorbed. Since the inventive compositions slow gastrointestinal transit (delays both gastric emptying and small intestinal transit) a more rapid dissolving dosage form is preferred.

Accordingly, the present invention provides pharmaceutical oral articles and enteral formulas that slow gastrointestinal transit and prolong residence time of a substance. The composition of the invention enhance dissolution, absorption, and hence bioavailability of pharmacologically active agents ingested concurrently therewith or subsequent thereto.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or

excipient suitable for enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used.

The active lipid is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of diseases.

Pharmaceutical compositions containing the active lipid may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups, elixirs or enteral formulas. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the

techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release. Other techniques for controlled release compositions, such as those described in the U.S. Pat. Nos. 4,193,985; and 4,690,822; 4,572,833 may be used in the formulation of invention pharmaceutical compositions.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The methods and compositions of the invention are most needed for pharmacologically active agents that have slow dissolution characteristics. Since the active agent is released slowly such as formulations that are now enterically coated or packaged in a sustained release form, there is great potential for the drug to be passed into the colon still incompletely absorbed. The role of the inventive compositions is to increase the gastrointestinal residence time to allow the poorly dissoluting drugs to be fully absorbed.

In one embodiment of the present invention, the pharmaceutical article is an enterically coated or a sustained release form that intestinal transit is slowed for a prolonged period of time. The pharmacologically active agent can also be packaged in an enterically coated or sustained release form so that it can also be released slowly. This combination would probably have the longest biologic activity and be favored if a high initial drug plasma peak is not desirable.

In an alternative embodiment, invention pharmaceutical article may be formulated for controlled release (enterically coated or sustained release form) whereas a rapid release formulation is contemplated for the pharmacologically active agent (tablet or capsule with rapid dissolution characteristics or composition in a liquid form). This simpler strategy would be used if the claimed composition is able to "hold" the active

drug in the proximal small intestine for a period long enough for complete absorption of the drug to take place and a high initial peak of the drug is desirable.

Another embodiment of the instant invention contemplates a rapid release formulation of the composition/article. This form would be administered following slow release of the pharmacologically active agent which is enterically coated or a sustained release form.

Also contemplated by the instant invention is the combination of a rapid release form of the composition/article and a rapid release of the pharmacologically active agent.

Accordingly, the methods and compositions of the instant invention can be combined with the existing pharmaceutical release technology to provide control over not only the gastrointestinal transit and residence time of a pharmacologically active agent, but also over the time of release of the active agent. More specifically, the combination of invention methods and compositions with existing release technology provides control over the multiple factors that influence intestinal absorption of a pharmacologically active agent. The ability to control such factors enables optimization of the bioavailability and ultimate therapeutic effectiveness of any pharmacologically active agent.

The following examples are intended to illustrate, but not limit, the present invention.

EXAMPLE I

Oleate and Oleic Acid Slow Upper Gut Transit and Reduce Diarrhea in Patients with Rapid Upper Gut Transit and Diarrhea

Rapid transit through the upper gut may result in diarrhea, maldigestion and absorption, and weight loss; and pharmacologic treatment with opiates or anticholinergics often is required. It was tested whether fatty acids could be used to slow upper gut transit and reduce diarrhea in patients with rapid transit and diarrhea.

In a preliminary study, five patients with persistent diarrhea for 3 to 22 months, (one each due to vagal denervation, ileal resection for Crohn's disease, and vagotomy and antrectomy, and two due to idiopathic causes) were studied. Each patient demonstrated rapid upper gut transit on routine lactulose breath hydrogen testing (or variations thereof measuring labelled carbon dioxide)(Cammack *et al. Gut* 23:957-961 [1982]). This test relies on the metabolism of certain carbohydrate materials (e.g. lactulose) by the microbial flora within the caecum. By generating gas which can be detected in the expired air, it is possible to make some estimation about the initial arrival of the administered material within the colon.

Each patient received orally in random order, 0, 1.6 or 3.2 g of sodium oleate in 25 mL Ensure (Ross), followed by 100 mL water. Thirty minutes after each dose of oleate, patients received 10 g lactulose orally, followed by 25 mL water. Breath samples were collected in commercially available breath testing bags (Quintron, Menomonee Falls, WI) every 10-15 minutes, and the hydrogen content of the samples was measured using a breath analyzer (Microlyzer Model 12, Quintron Instruments, Menomonee Falls, WI), calibrated against gas samples of known hydrogen concentration. With a syringe, a 40-mL sample of the expired breath was withdrawn from the collection bag and analyzed immediately for hydrogen concentration (ppm). The hydrogen concentration value from each sample was plotted against time. Upper gut transit time was defined as the time in minutes from ingestion of lactulose (t_0) until a rise of H_2 of

>10 ppm. Data were further analyzed using 1-way repeated measures analysis of variance (ANOVA).

Results (mean ± SE):

Oleate (g)	0	1.6	3.2
Transit time (min)	46 ± 8.6	116 ± 11.1	140 ± 11.5

Upper gut transit was significantly prolonged by oleate in a dose-dependent fashion ($p < 0.005$, significant trend). During prolonged ingestion of oleate 15-30 minutes prior to meals, all patients reported reduced diarrhea. The patient with Crohn's disease reported complete resolution of chronic abdominal pain as well as post prandial bloating and nausea, and gained 22 lbs. In addition, the patient with vagotomy and antrectomy reported resolution of postprandial dumping syndrome (flushing, nausea, light-headedness).

The effect of an active lipid on transit time was determined in 8 normal human subjects (1 male and 7 females with a mean age of 35 ± 2.6 years [SE]) and 45 patients (20 males and 25 females with a mean age of 49.1 ± 2.5 [SE], age range from 18 to 90 years) with chronic diarrhea (i.e., continuous diarrhea for more than two months) associated with a wide variety of diagnoses and conditions (e.g., Crohn's disease; irritable bowel syndrome; short bowel syndrome; Indiana pouch; AIDS; ulcerative colitis; vagotomy; antrectomy; ileostomy; partial and complete colectomy; colon cancer; diabetes mellitus type 1; pancreatic insufficiency; radiation enteropathy; esophagectomy/gastric pull-up; total and subtotal gastrectomy; gastorjejunostomy), made by referring gastroenterologists. The method was the same as described above, except oleic acid (Penta Manufacturing, Livingston, NJ) replaced sodium oleate in 50 mL of Ensure emulsion. All subjects refrained from taking antibiotics for at least two weeks before each testing date and during stool measurement periods. Patients were also instructed to refrain from anti-diarrheal drugs, laxatives, somatostatin analogues or anticholinergics for at least 48 hours before each test. In both the normal and patient groups, there was a significant slowing of upper gut transit time in response to oleic acid, as summarized below ($p < 0.001$):

	Transit time (min) (mean ± SE)		
Oleic Acid (g)	0	1.6	3.2
Normal	105.2 ± 12.1	116 ± 11.1	140 ± 11.5
Patients	29.3 ± 2.8	57.2 ± 4.5	83.3 ± 5.2

Continuing oleic acid treatment at home was offered to "responders" (i.e., patients who experienced a greater than 100 % increase in baseline transit time with 3.2 g oleic acid). Of the 36 responders out of the original 45 patients, 18 provided records of stool volume and frequency on- and off- treatment for comparison. The inconvenient and unappealing nature of stool collection and measurement were the primary reasons reported by responders who chose not to participate in stool collection. After completing a set of three preliminary breath hydrogen tests, each participating responder was asked to refrain from taking oleic acid for two days in order to measure off-treatment stool output for a 24-hour period. Patients were issued a stool pattern record form and a stool collection container with graduated volume markings to record the frequency and volume of bowel movements. After two days without oleic acid, each patient took 3.2 g of oleic acid mixed with 25 mL of Ensure emulsion three times a day, 30 minutes before breakfast, lunch and dinner. After taking oleic acid for two days, patients recorded stool output for another 24-hour period. With this oleic acid emulsion treatment, stool frequency decreased from 6.9 ± 0.8 to 5.4 ± 0.9 bowel movements per 24-hour period ($p < 0.05$), and stool volume decreased from 1829.0 ± 368.6 to 1322.5 ± 256.9 per 24-hour period ($p < 0.05$). A slight and transient burning sensation in the mouth or throat was the only adverse effect reported by any patient taking the oleic acid treatment.

These experiments demonstrate that active lipids, such as oleate and oleic acid, are effective in slowing upper gut transit in a dose-dependent manner and reduce diarrhea among patients with rapid transit and diarrhea. This novel treatment is effective in other chronic diarrheal conditions associated with rapid transit.

EXAMPLE II

Fat in Distal Gut Inhibits Intestinal Transit More Potently Than Fat in Proximal Gut

In 4 dogs equipped with duodenal (10 cm from pylorus) and midgut (160 cm from pylorus) fistulas, intestinal transit was compared across an isolated 150 cm test segment (between fistulas) while 0, 15, 30 or 60 mM oleate was delivered into either the proximal or distal segment of the gut as a solution of mixed micelles in pH 7.0 phosphate buffer at 2 mL/min for 90 minutes. The segment of gut not receiving oleate was perfused with buffer at 2 mL/min. 60 minutes after the start of the perfusion, ~20 μCi of ^{99m}Tc-DTPA (diethylenetriaminepentaacetic acid) was delivered as a bolus into the test segment. Intestinal transit was then measured by counting the radioactivity of 1 ml samples collected every 5 minutes from the diverted output of the midgut fistula.

Intestinal transit was calculated by determining the area under the curve (AUC) of the cumulative percent recovery of the radioactive marker. The square root values of the AUC (Sqrt AUC), where 0 = no recovery by 30 minutes and 47.4 = theoretical, instantaneous complete recovery by time 0, were compared across region of fat exposure and oleate dose using 2-way repeated measures ANOVA.

	Oleate dose (mM) (mean ± SE)		
Region of fat exposure	15	30	60
Proximal 1/2 of gut	41.6 ± 1.4	40.6 ± 10.2	34.4± 3.0
Distal 1/2 of gut	25.6 ± 1.4	18.9 ± 1.5	7.0 ± 3.8

Control: buffer into both proximal and distal 1/2 of gut = 41.4 ± 4.6.

These experiments demonstrate that intestinal transit is slower when fat is exposed in the distal 1/2 of gut (region effect $p < .01$). These experiments also demonstrate that oleate is effective to inhibit intestinal transit in a dose-dependent fashion (dose effect, $p < .05$); and that dose dependent inhibition of intestinal transit by oleate depends on the region of exposure (interaction between region and dose, $p < .01$).

EXAMPLE III

Case Studies Showing Successful Treatment of Diarrhea With Oleic Acid

Postgastrectomy Dumping Syndrome. The patient was a 57 year old female with a history of subtotal gastrectomy and gastrojejunostomy for peptic ulcer and gastric cancer. Symptoms on presentation of nausea, cramping pain, lightheadedness, bloating and explosive diarrhea occurring after every meal were consistent with severe dumping syndrome. These symptoms persisted despite aggressive medical therapy including the use of tincture of opium and anticholinergics. Her upper gut transit times were (min) 16 (0 g oleic acid), 99 (1.6 g oleic acid) and 108 (3.2 g oleic acid). After one pre-meal treatment with oleic acid (3.2 g mixed with 25 mL of Ensure), this patient reported immediate benefit. With continued treatment with oleic acid (3.2 g mixed with 25 mL of Ensure, gravy or other comestible emulsion three times a day, 30 minutes before breakfast, lunch and dinner), she had only rare episodes of dumping symptoms (only about once per month). Her weight increased from 118 to 130 lbs, and bowel movements decreased from 4 to 5 liquid to 2 to 3 formed bowel movements per day.

Diarrhea-Predominant Irritable Bowel Syndrome. The patient was a 39-year old male with a history of adolescent-onset, persistent diarrhea. After a routine gastrointestinal work-up failed to provide an explanation for his symptoms, he was given the diagnosis of diarrhea-predominant irritable bowel syndrome. He presented with complaints of excessive gas, postprandial bloating, diarrhea and urgency, and 3 to 7 liquid bowel movements per day. His upper gut transit times were (min) 30 (0 g oleic acid), 117 (1.6 g oleic acid) and 101 (3.2 g oleic acid). With continuing oleic acid treatment as described above, he reported his bowel frequency reduced to a single, solid bowel movement per day. He also reported complete relief from the symptoms of gaseousness, bloating and rectal urgency.

History of Ileal Resection. The patient was a 64 year old female who had chronic diarrhea since 1990, when she underwent an intestinal resective surgery to create an Indiana Pouch from her ileum to drain her right kidney. After the surgery, the patient had approximately 4 to 6 watery bowel movements per day with a 24-hour stool volume of 950 mL. At the time of presentation, she had reported a weight loss of 20 lbs over the previous 6-month

period despite greater than normal appetite and food intake. Her upper gut transit times were (min) 60 (0 g oleic acid), 68 (1.6 g oleic acid) and 148 (3.2 g oleic acid). With continuing oleic acid treatment as described above, her 24-hour stool volume decreased to 200 mL, and her stool frequency was reduced to a single solid bowel movement daily.

Short Bowel Syndrome. The patient was a 38-year old male with a thirty-year history of Crohn's disease. Five intestinal resections had resulted in a remainder of about 100 cm of small intestine and descending colon. He presented at 93 lbs; with severe difficulties with oral intake, and was readied with placement of a central line for life-long total parenteral nutrition (TPN). He was experiencing more than 20 bowel movements per day, with pain, bloating and nausea at each meal. Baseline upper gut transit time was 14 min. His transit time was prolonged to 47 and 158 min with 1.6 and 3.2 grams of oleic acid, respectively. After the patient began taking oleic acid three times a day, his stool volume decreased during the first 24-hour period from 3400 mL to 1400 mL. Over the course of 2 months of oleic acid treatment, he gained 30 lbs without TPN, and he was able to enjoy an unrestricted diet without symptoms.

A 42-year-old female patient with a history of Crohn's disease and intestinal resective surgeries developed severe diarrhea after her latest intestinal resection and iliostomy. Before treatment, her stool volume was about 1025 mL per day. With oleic acid (6.6 grams in 50 mL of Ensure), her stool volume decreased to 600 mL per day.

EXAMPLE IV

Administration of Active Lipid Increases Drug Bioavailability

Relatively rapid basal upper gut transit in Patients with Inflammatory Bowel Disease (IBD). The mean upper gut transit time for IBD patients (n=18) at 0 grams of oleic acid was 79.1 $\pm$ 11.0 min., compared to 118.7 $\pm$ 9.8 min for normal subjects (n = 5)($p = 0.04$, t-test).

Measurement of basal drug bioavailability. The hypothesis that the bioavailability of oral drug is lower in IBD patients was tested by measuring serum levels of acetaminophen after oral administration of 1000 mg of this drug in a liquid formulation. Acetaminophen was chosen, because it is absorbed rapidly and almost exclusively and entirely in the proximal intestine; it is safe in a therapeutic dose range; and is only minimally bound to plasma proteins. After subjects ingested the drug, periodic samples of blood were collected from a plastic tube inserted into a vein in each subject's arm. The blood was then analyzed spectrophotometrically for concentration of acetaminophen. Peak plasma level, time to peak concentration and area under the curve (AUC; representing the plasma acetaminophen concentration over time) were derived from these data. Relative drug bioavailability was determined by comparing AUC values. In control experiments without oleic acid, IBD patients had a smaller AUC than normal subjects, consistent with lower acetaminophen bioavailability; the mean AUC for normal patients (n = 5) was 1438.9 ± 208.5. The mean AUC for IBD patients (n=18) was 687.3 ± 98.2. ($p < 0.05$, t-test).

Active lipid increases upper gut transit time and drug bioavailability. The mean transit time for normal subjects (n= 5) at 0 grams of oleic acid was 118.7 ± 9.8 min, at 4 grams of Oleic acid was 136.0 ± 15.4 min. (P <0.05, t-test). The mean AUC for normal subjects at 0 grams of oleic acid was 1438.9 ± 208.5; at 4 grams of oleic acid it was 1873.3 ± 330.5 ($p < 0.05$, t-test). The mean transit time for IBD patients (n =18) at 0 grams of oleic acid was 79.1 ± 11.0 min; at 4 grams of oleic acid it was 114.6 ± 16.0 min. ($p <$ 0.05, t-test). The mean AUC for IBD patients at 0 grams of oleic acid was 687.3 ± 98.2; at 4 grams of oleic acid it was 1244.9 ± 250.4. ($p < 0.05$, t-test). These data show that oleic acid slowed gut transit time and increased bioavailability of the drug in both normal and IBD groups.

Although the invention has been described with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific embodiments taught hereinabove are only illustrative of the invention. It should be

understood that various modifications can be made without departing from the spirit of the invention.